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Risk Assessment of Side Effects From Copper Vapor and Argon Laser Treatment: The Importance of Skin Pigmentation

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Background and Objective: **Epidermal melanin is a limiting factor for obtaining beneficial results in dermatological treatment of vascular malformations. The aim of our study was to predict the highest laser intensity and energy fluence which can be applied to skin with different degrees of pigmentation before side effects are induced.**

Study Design/Materials and Methods: **Thirteen human volunteers with different degrees of skin pigmentation were laser-treated on the inside of the brachium with an argon laser (AL, 488 nm and 514.5 nm) and a copper vapor laser (CVL, 578 nm), both connected to a Hexascan. Three input intensities were used, 0.7, 1.0, and 1.3 W. Pulse duration was kept constant at 200 msec, resulting in hexascan fluences of 14.1, 20.2, and 26.2 J/cm^2. At the 6-month assessment it was noted whether pigmentary changes or scarring were clinically absent or present. The results were analysed by logistic regression.**

Results: **We found that pretreatment pigmentation percentage and laser intensity were significant risk factors of inducing side effects ($P < .001$), whereas it was without significant importance whether the AL or the CVL was used ($P > .05$). Contour lines of 1, 2.5, 5, 10, 25, and 50% risk levels of inducing clinically recognizable pigmentary changes and scarring were calculated. Pigmentary changes occurred at a significantly lower intensity level than skin texture changes ($P = .006$).**

Conclusion: **On basis of our results, we recommend assessment of skin pigmentation prior to laser treatment with the CVL and the AL, and we recommend that the illustrated risk levels are taken into consideration. Lasers Surg Med 20:84–89, 1997**

Key words: cicatrix; hemoglobin; hyperpigmentation; adverse effects of lasers; skin pigmentation

INTRODUCTION

The treatment of port wine stains, telangiectasia, and other dermatological vascular malformations was greatly improved when the argon laser was introduced in dermatology (argon laser [AL], 488 nm and 514 nm, blue-green light). However, an important progress has been the development of laser systems that are capable of delivering yellow light (dye laser 577 nm and 585 nm; copper vapor laser [CVL], 578 nm) [1]. These yellow laser systems possess a potential advantage to blue-green laser systems, since light from the yellow spectrum is absorbed in a higher degree by haemoglobin and in a lower degree by the competitive epidermal melanin [2,3].

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Neither the AL nor the CVL meet the requirements for selective photothermolysis, which is responsible for a selective destruction of target tissue while minimizing or avoiding non-selective thermodamage to surrounding nontarget tissue. However, both laser types are commonly used for treatment of vascular malformations, and a great deal of experience has been built up with these two laser systems [4–8]. Therefore these lasers, and especially the CVL, whose wavelength matches one of the peaks of the absorption curve of haemoglobin, will be used in future.

Clinical studies have supported the theoretical superiority of the CVL as compared with the blue-green AL: Beneficial results after treatment of port wine stains and facial telangiectasia with the CVL have been described [8–10], and it has been reported that fewer side effects (pigmentary and texture changes) occur with the CVL as compared with the AL [8]. Side effects depend on both physical properties of the laser system and on biological properties of the skin, i.e., the degree of epidermal pigmentation [11], anatomical location [13], and type of vascular malformations [7]. The aim of this study was to predict the highest laser intensity, which can be applied to skin with a given degree of pigmentation before side effects are induced.

SUBJECTS AND METHODS

Human Volunteers

The study included 13 normal-skinned human volunteers (9 males and 4 females) with ages from 23 to 46 years and skin types ranging from type I to type V. (Two volunteers skin type I, two type II, and three volunteers with each of the types III, IV and V). The volunteers gave their informed consent to join the investigation, and the laser treatment was performed after infiltration anaesthesia with lidocaine. Treatment was performed in six hexagonal areas on the inside of the brachium where three areas were treated with a CVL and three were treated with an AL.

Technics

The CVL, Multilase, (PBI Medical, Denmark) and the AL (Meditech, Germany) were used in connection with a microprocessor controlled handpiece, a Hexascan Mark I device (Prein & Partners, Ferney-Voltaire, France). Hereby the laser pulses were applied to the skin from a fixed distance and in a special sequence which allows cooling time between each spot exposure and a high degree of uniformity of the treated areas [14,15]. The Hexascan has an indicator accuracy of ± 0.05 Watts. The CVL operates in a quasi-continuous mode, producing a rapid train of pulses (8,400 pulses/sec ~ 8.4 kHz) at 578 nm, yellow band. The AL operates in a continuous mode, emitting combined blue-green light at 488 and 514 nm. Three input intensities were used, 0.7, 1.0, and 1.3 W/spot. The beam diameter was 1 mm (spot area 0.785×10^{-2} cm), which resulted in irradiances of 89, 127, and 166 W/cm^2. The pulse duration was kept constant at 200 msec, making us operate with the following calculated fluences in a spot: 17.8, 25.5, and 33.1 J/cm^2. The hexascan was adjusted to deliver 127 spots, distributed over a total hexagonal exposure area of 1.26 cm^2, which resulted in hexascan fluences of 14.1, 20.2, and 26.2 J/cm^2. Hexascan fluences (J/cm^2) were 1.3 times lower than calculated spot fluences (J/cm^2), since the single hexascan-emitted round spots were placed side-by-side without overlapping and some interjacent unexposed skin was included in the hexascan fluence. Laser intensities were controlled by a power-meter (Analogue Power Read Out 25 APR. Power Meter Head 25 V-VIS, Photon Control).

Skin Reflectance

The degree of pigmentation in the six treated areas was measured before the laser treatment. Skin pigmentation measurements were performed with an instrument for non-invasive measurements of skin pigmentation and skin redness independently. The instrument, the UV-Optimize, measures the reflection of green and red light by skin reflectance at 550 and 660 nm. Equations for calculating the percentages of pigmentation and redness are built into the instrument. One measurement takes about 10 sec [16]. In this study the pigmentation percentage was used. The values were stated in pigmentation percentage, the scale ranging from 0 to 100%. One hundred percent represents no reflection, corresponding to maximal black skin colour; 0 represents the most fair-skinned person.

Experimental Design and Statistics

The laser-induced skin reactions have in former studies been evaluated clinically for acute and long-term changes and graduated into clinical scoring systems [11]. On basis of the 6-month findings we subsequently performed a registration of whether pigmentary changes or scarring were clinically recognizable in each of the laser-

TABLE 1. Frequencies of Induced Side Effects Are Shown for the Three Laser Intensities/Fluences Used as the Number of Individuals Having Obtained Skin Pigmentary Changes and Scarring Versus the Total Number of Participating Volunteers in the Study*

		Frequencies of pigmentary changes		Frequencies of scarring	
Intensity (W)/fluence (J/cm^2)	Pretreatment pigmentation, %	Pretreatment pigmentation ⩽22%	Pretreatment pigmentation >22%	Pretreatment pigmentation ⩽22%	Pretreatment pigmentation >22%
0.7 W/14.1 J/cm^2	22 (9–45)	1/13	8/13	0/13	4/13
1.0 W/20.2 J/cm^2	22 (9–46)	7/13	12/13	1/13	11/13
1.3 W/26.2 J/cm^2	22 (12–49)	11/13	13/13	11/13	13/13

*The distribution of pretreatment skin pigmentation % is shown for the three laser intensities, median (range). No distinction is performed between the CVL and the AL, since no differences were observed between these lasers.

treated areas. No grading of induced side effects was performed; it was just noted whether pigmentary changes or skin texture changes were absent or present. These binary results were analysed by logistic regression [17], which describes the risk of inducing side effects after laser therapy as a mathematical function of the risk-variables in the model, i.e., pretreatment pigmentation, laser intensity, and lasertype. The Wilcoxon test was used to compare the highest laser intensities, which did not induce pigmentary changes and scarring. The P values were considered significant at ⩽.05.

RESULTS

Frequencies of induced side effects in the form of pigmentary changes and scarring are shown in Table 1. It appeared that the frequencies increased with increasing pretreatment pigmentation percentage and with increasing laser intensity.

The logistic regression analyses demonstrated that the variables pretreatment pigmentation percentage ($P < .001$) and laser intensity ($P < .001$) were significant risk factors of inducing side effects, whereas it was of no importance for the occurrence of side effects whether the CVL or the AL was used ($P > .05$).

The results from the logistic regression analyses are depicted graphically in Figures 1 and 2. It was observed that the risk of inducing pigmentary changes and scarring 6 months after laser treatment with the CVL and the AL increased with more heavily pigmented skin color and with the use of increasing laser intensities. The contour lines represent combinations of pretreatment pigmentation degrees and laser intensities, which result in given risk levels of 1, 2.5, 5, 10, 25, and 50% to induce clinically recognizable pigmentary changes and scar formation. Comparing Figures 1 and 2, it appears that side effects in the form of pigmentary changes are induced at a lower laser intensity level than scarring for skin with the same degree of pigmentation. For instance a person with a pretreatment pigmentation of 17% has a 5% risk of scarring and just below 50% risk of obtaining pigmentary changes after laser treatment with 1.0 Watt with either of the two used laser types, whereas a pale person with a pretreatment pigmentation of 10% has only a 10% risk of obtaining pigmentary changes, and no significant risk of scarring. The Wilcoxon test revealed that the highest laser intensities, which did not induce pigmentary changes, were significantly lower than the highest laser intensities, which did not induce scar formation ($P = .006$).

Clinical skin reactions covered a broad spectrum: Scarring included from just-visible texture changes, to atrophy, hypertrophy, and skin shrinkage. Pigmentary changes included both hyper- and hypopigmentation, the hypopigmentation representing the heaviest skin reaction.

DISCUSSION

Our study established 1, 2.5, 5, 10, 25, and 50% risk levels of inducing side effects 6 months after treatment with the AL and the CVL for normal-skinned individuals with a varying degree of skin pigmentation. Pigmentary changes occurred at lower intensity levels than scarring, and we found the distance between the scarring contour lines to be narrower than the contour lines to induce pigmentary changes, which is illustrated in Figures 1 and 2. These findings express that scarring easily is induced when the limit of inducing pigmentary changes is reached.

Side effects after laser treatment of vascular

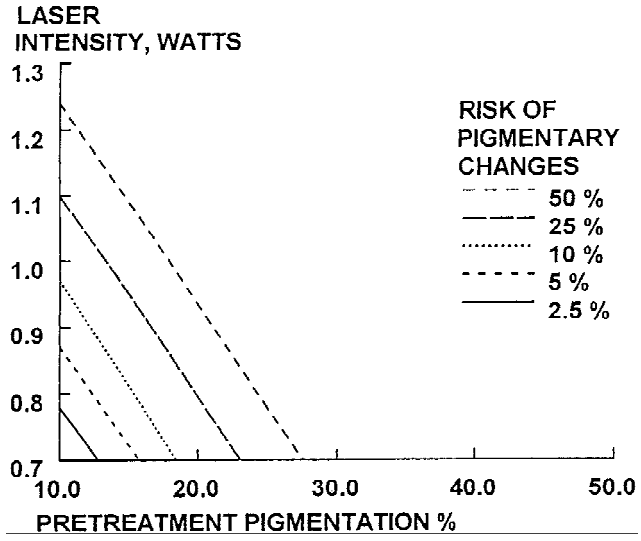

Fig. 1. Contour lines for given risks of inducing pigmentary changes. The lines are calculated from the estimated logistic model: Ln (P/(1 – P)) = –12.599 + 0.249 · X + 8.222 · Y, where P is the risk of inducing pigmentary changes, X is the pretreatment pigmentation %, and Y is the laser intensity in Watts. The numerical coefficients are determined by the logistic regression analysis.

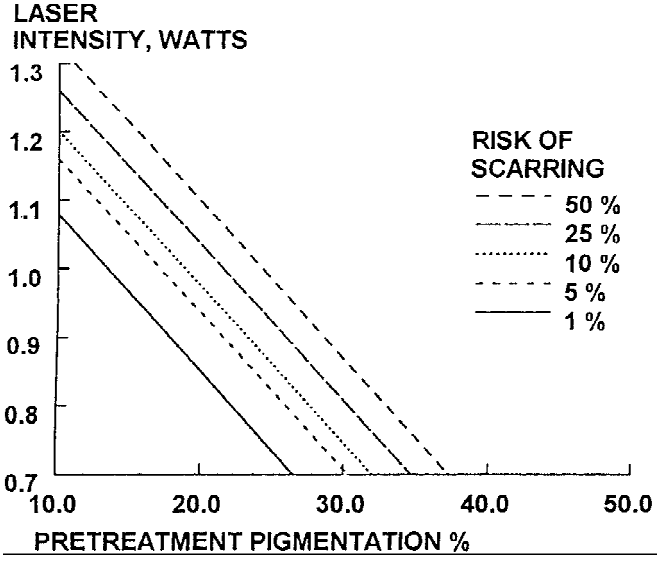

Fig. 2. Contour lines for given risks of inducing scarring. The lines are calculated from the estimated logistic model: Ln (P/(1 – P)) = –29.016 + 0.427 · X + 18.735 · Y, where P is the risk of inducing scarring, X is the pretreatment pigmentation %, and Y is the laser intensity in Watts. The numerical coefficients are determined by the logistic regression analysis.

malformations are in theory due to three different mechanisms, all of which result in nonspecific energy deposition: a) direct and competitive absorption by epidermal melanin, b) thermal diffusion away from the absorbing chromophores, primarily melanin and hemoglobin, and c) scattering effects, which indirectly increase epidermal and dermal nonspecific injury. The importance of these mechanisms are not to be considered of equal importance for skin with vascular malformations and for skin with normal dermal vessels, since skin with a low content of haemoglobin has a low specific intravascular energy absorption, resulting in a higher degree of unspecific energy deposition due to an increase in the depth of optical penetration and due to optical scattering, mainly by collagen fibers [2,18]. The side effects may thus be of a higher degree in the normal-skinned model as compared with side effects obtained from laser treatment of vascular malformations, and therefore, reservations have to be taken to this normal-skinned model. Nevertheless, the range of energy fluences used in our study agrees with the current treatment parameters for vascular lesions (16–26 J/cm^2; 488/514 and 585 nm) and for melanocytic disorders (10–15 J/cm^2, 514 nm) [14,15,19]. It is noteworthy, anyway, that the 514-nm wavelength has been used to remove epidermal melanocytic disorders at fluences of 10–15 J/cm^2; as well as, application of these fluences in our study has been shown to provoke hyperpigmentation as a side effect. We ascribe this paradox to the fact that two different mechanisms are involved in the processes of removing and provoking pigmentation: A) Target specificity is considered the main responsible for removal of melanocytic disorders, whereas B) the skin's ability to increase pigmentation, i.e., skin type, is considered the main responsible factor for occurrence of hyperpigmentation as a side effect. Moreover, we have found skin type to be related to occurrence of immediate pigment darkening, which may represent photo-oxidation of pre-existing melanin, since we have experienced immediate pigment darkening in darker skin types but not in fair-skinned persons (unpublished data).

Clinical outcome and side effects have been reported to depend on biological, interindividual variables such as lesional color, anatomical location, skin thickness, and epidermal pigmentation: Noe et al. [7] described dark-colored port wine stains to respond with a better clinical outcome after argon laser therapy than pale lesions, just as Dinehart et al. [4] reported the copper vapor laser to be advantageous in the treatment of dark purple, hypertrophic port wine stains. Furthermore, Renfro and Geronemus [13] reported that centro-

facial lesions and lesions involving dermatome V_2 in adults and children respond less favourably than lesions located elsewhere on the neck and head and that structural characteristics of the dermis or variations in skin thickness might account for these findings. Additionally, transmission of human epidermis and stratum corneum has been examined in the ultraviolet and visible wavelengths [20], and it was found that increasing thickness of stratum corneum and epidermis resulted in a decreased transmission. However, the importance of varying epidermal thickness for the clinical outcome after dermatological laser treatment is not clarified. Therefore, we tried in our study to eliminate differences in skin thickness, since laser exposures were performed on the inside of brachium, where epidermal skin thickness is considered constant. Skin pigmentation has been reported to constitute a main limitation to the final outcome after dermatological laser treatment in histological [21,22] and clinical studies [11] and in a case report [23]. However, it is unknown whether constitutional or acquired pigmentation is of the same importance to the final result. In our study we only included volunteers with varying degrees of constitutional skin pigmentation.

Physical laser parameters are of importance to selective vascular injury, as well, i.e., wavelength, intensity, pulse duration, spot size, and a continuous, pulsed, or quasi-continuous mode of action [18,24-27]. In our study we varied input laser intensities, resulting in different laser fluences, whereas other physical laser settings were fixed and kept similar when possible. However, none of the two laser systems in our study meet the requirements for selective photothermolysis, which constitutes the basis for the approved and recommended flashlamp-pulsed tunable dye laser, operating at a wavelength of 585 nm and with a pulse duration of 450 μsec [19]. The AL deviates from selective photothermolysis by operating at wavelengths of 488 nm and 514 nm in the blue-green spectrum, which does not coincide with one of the three absorption peaks of oxyhemoglobin at 418, 540, and 577 nm. Furthermore, both the AL and the CVL deviate by operating with pulse lengths in the range of milliseconds instead of in microseconds. However, the pulse lengths of 200 msec in our study were similar for the two laser types, whereas the modes of action differed for the two laser types: The AL operates in a continuous mode, whereas the CVL operates in the quasi-continuous mode, in which pulses are emitted in a train of ultrashort pulses of 20 nsec each, a repetition rate so high that the pulses are additive and react in tissue as if they were a continuous beam [4].

We have estimated the highest possible laser intensity that normal-skinned persons with different degrees of constitutional skin pigmentation can be treated with before side effects are induced. However, the results from our study are obtained at selected physical laser settings, and therefore, are only to be used to predict the highest possible and optimal laser intensity when similar physical settings are used.

On the basis of this study we recommend a pretreatment measurement of pigmentation to be performed prior to laser treatment with the CVL and the AL and to be taken into consideration when physical laser settings are chosen.

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